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Towards Accurate Predictions of Binding Affinities: The Simulated Scaling Based Free Energy Method

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1 Introduction

Among various available computational methods, free energy simulation technique [1-7], based on molecular dynamics or Monte Carlos simulations, is unique; this is, if simulation time permits and energy potential is reasonably accurate, it can ultimately lead to quantitative predications of free energy values corresponding to the processes of interest, in particular the binding processes involving drugs and other biologically relevant agents because this method is built upon solid statistical mechanical theories. Unfortunately, with the present computing power and in particular the state-of-the-art free energy simulation algorithms, reaching adequate simulation time for nice free energy convergence, is still quite challenging.

Facing such challenge and also great opportunity, we have been motivated to consider solving these problems. One of our recent developments, the simulated scaling (SS) based method [8], shows intriguing efficiency and robustness. The simulated scaling based free energy simulation method originated from stepwise generalizations of the simulated tempering method. Specifically, at the first step, the temperature space random walk in simulated tempering was generalized to be the potential scaling parameter space random walk based on the modified potential: $U = \lambda U_s + U_e$, where the original energy potential U_0 is decomposed to U_s and U_e, and the scaled energy potential U_s represents the energy terms determining the local conformations of a region of interest. Thereby, the developed algorithm, named by us as the simulated scaling method, allows local sampling to be enhanced in the conformational region described by U_s. In order to realize simultaneous improvement in phase space overlap sampling for free energy simulations, we further generalized the SS method and made it coupled with the dual-topology alchemical free energy simulation setup. Via this generalization, both phase space overlap sampling and conformational sampling problems can be synergistically dealt with. As discussed in our early work, the SS method can also be employed with the single-topology setup, in which A and B share the same set of coordinates; in this setup, conformational sampling problem cannot be ensured as robustly as in the dual-topology setup.

In the following sections, we will describe the SS based free energy method and its extension in the simulations based on quantum mechanical potentials.

2 Simulated Scaling (SS) Method for Localized Enhanced Sampling

For a system with the potential $U_0 = U_s + U_e$, where U_s represents the energy terms determining local conformations in an interested region and U_e represents the rest of en-

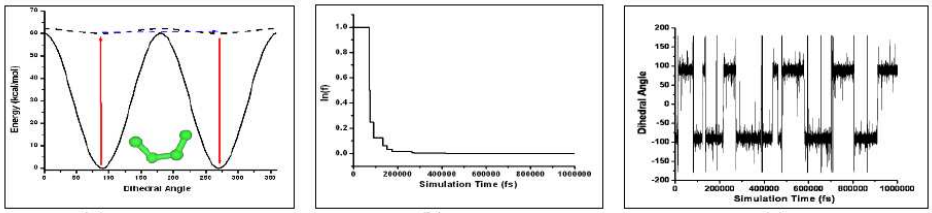
vironmental energy terms. Usually, because of the existence of large energy barriers, converged traveling among various energy minima via regular canonical sampling is time-consuming, sometimes even impossible within currently computer-reachable simulation timescales. To overcome this problem, we can build an expended ensemble with the scaled potential $U = \lambda_m U_s + U_e$, where the dimensionality of the system is extended to 3N+1 (N is the number of real particles) with an additional one-dimension dynamic species λ_m. The canonical traveling in the λ_m space can be realized via hybrid Monte Carlo method [9]. Based on the constructed scaled potential, an acceptance probability for a move from λ_0 to λ_1 can be set as

$$\begin{aligned} p^0_{acpt}[(\lambda_0 \rightarrow \lambda_1)] &= \min\{1, \exp[-\beta[\lambda_1 U_s + U_e) - (\lambda_0 U_s + U_e)]]\} \\ &= \min\{1, \exp[-\beta(\lambda_1 - \lambda_0)U_s]\} = \min\left\{1, \exp\left[- \beta\Delta\lambda\frac{\partial U}{\partial \lambda}\right]\right\}, \end{aligned} \tag{1}$$

in which energy derivative $\frac{\partial U}{\partial \lambda}$ is equal to U_s and scaling parameter change $\Delta\lambda$ is equal to $(\lambda_1 - \lambda_0)$. In this way, the moves in the λ_m space will allow possibly efficient barrier crossing, detoured through the path with λ_m decrease from 1 (effective lowering the energy barriers), barrier crossing (with lower energy barriers), and λ_m increase (returning to 1). However, the probability distribution $\rho(\lambda_m)$ in the λ_m space is determined by the λ_m-dependent free energy profile (potential of mean force), roughness of which very possibly hinders an efficient λ_m move. In order to make a λ_m random walk possible, as discussed in last section, a weight function $a(\lambda_m)$ can be introduced to flatten the λ_m distribution by the application of a biased acceptance probability

$$\begin{aligned} p^{biased}_{acpt}[(\lambda_0 \rightarrow \lambda_1)] &= \min\left\{1, \exp\left(- \beta\Delta\lambda\frac{\partial U}{\partial \lambda}\right)\frac{\exp[a(\lambda_0)]}{\exp[a(\lambda_1)]}\right\} \\ &= \min\left\{1, \exp\left(- \beta\Delta\lambda\frac{\partial U}{\partial \lambda}\right)\frac{f(\lambda_0)}{f(\lambda_1)}\right\}, \end{aligned} \tag{2}$$

in which $\exp[a(\lambda_m)]$ is defined as biasing probability function $f(\lambda_m)$. Thereby, the weight function $a(\lambda_m)$ can be recursively updated with the modification of $f(\lambda_m)$. Specifically, in order to efficiently flatten the λ_m histogram, the updating scheme in the Wang-Landau algorithm [10] is adopted here. When each time a λ_m state is visited after a Monte Carlo acceptance judgment, we update the corresponding biasing probability function $f(\lambda_m)$ using a modification factor $f > 1$, i.e., $f(\lambda_m) \rightarrow f(\lambda_m)/f$. The initial modification factor f_0 can be set as a large value in order for the system to quickly visit all the λ_m states, defined in a certain range $[\lambda_{\min}, \lambda_{\max}]$. This large modification factor f_0 is kept till λ_m random walk results in a "flat" accumulated histogram $H(\lambda_m)$. It is noted that the "flatness" judgment is based on a criteria of whether all the accumulated histograms $H(\lambda_m)$ are not less than a large percentage (80% is often used in the Wang-Landau multi-canonical algorithm) of the average histogram $\langle H(\lambda_m)\rangle$. Then before the next round of λ_m random walk, this modification factor f is reduced to a finer one, updated by a monotonically decreasing function (here $f_{i+1} = \sqrt{f_i}$ is used) and $H(\lambda_m)$ is reset to zero. Following this procedure, a number of cycles will be run continuously till the modification factor is extremely small. In the present development, we can also take a variation by switching



(a) (b) (c)

Figure 1. (a) Torsional potential for the "butane-like" molecule used in model system 1. Black curve represents the unscaled potential for this "butane-like" molecule; dash line represents a scaled potential. (b) Time evolution of during the simulation. (c) Dihedral angle change with the progress of simulation.

this modification factor f to be 1 when it is smaller than a pre-set cutoff value in order to obtain meaningful non-history dependent ensemble. As we will illustrate, the present simulated scaling algorithm shows superior updating efficiency in obtaining converged weight function $a(\lambda_m)$.

Illustrative Example: A "Butane-Like" Molecule. It only has bond, angle and dihedral terms in its potential. Bond and angle terms of this molecule are treated with the CHARMM "Butane" parameters as U_e term. Its dihedral term is set as a double-well potential: $30(1 + \cos(2x))$ kcal/mol, which has a high energy barrier (60 kcal/mol) and so almost exclusively only a λ_m tunneling mechanism (Figure 1a) can enables jumps between the two energy wells at 300 K. Here, the dihedral potential acts as U_s term, which is scaled by λ_m. In the simulated scaling method, facilitated by a λ_m random walk, such barrier crossing is guaranteed, as shown in Figure 1c, through a tunneling mechanism (Figure 1a); this tunneling mechanism [11] is realized by at least three basic steps of moves in the expended coordinate system: a λ_m decrease (solid arrow), physical energy barrier crossing in low λ_m potential (dash arrow), and a λ_m return (solid arrow).

3 Free Energy Simulations with Synergistic Localized Enhanced Sampling Treatments

In the improvement of the free energy simulation techniques, conformational sampling and free energy convergence (even independent of conformational sampling) are two major issues, although these two issues have been mainly discussed as independent topics. There is lack of discussion on how to efficiently deal with these two problems simultaneously, which is required to quickly and reliably obtain the free energy differences (i.e., rather than the precise pseudo-converged values corresponding to certain trapped local conformations).

Usually, an enhanced sampling method is designed to efficiently obtain the ensemble information on certain target physical states. Several accessory states (such as the ones with varied temperatures or Hamiltonians) can be introduced to efficiently propose the structures (to effectively cross the energy barriers) for the target state sampling. Conventionally, the measure of the "conformational sampling" efficiency is purely based on the results from the obtained target state ensembles. However, the accessory states can be use-

ful intermediate states to provide decent phase space overlaps to bridge the two end target physical states for the free energy evaluations. Therefore, we realize that in contrast to the "conformational sampling" problem, the sampling design for the free energy simulation also requires careful consideration of the accessory state ensembles. For free energy simulations, the sampling strategy should be designed with this special concern in mind, because various "conformational sampling" methods may have different level of efficiency in providing an appropriate set of the accessory state ensembles for the evaluation of the free energy difference.

Based on the above thought, an approach is proposed towards two goals: robustly enhanced canonical sampling, for which the accessory state ensembles are designed, and simultaneous quick free energy convergence, facilitated by the decent phase space overlaps provided by these accessory ensembles. Specifically, we propose a dual-topology alchemical simulated scaling (DTA-SS) method, here λ_m plays double roles, viz. 1) as the label of the intermediate state to improve the phase overlap along the alchemical direction; and 2) synergistically as an effective temperature label to enhance the SS sampling efficiency.

Theoretical Design of the Method. The scaled energy function can be rewritten in the dual-topology hybrid potential form, which is usually utilized in free energy simulations, as shown below

$$U = (1 - \lambda_m)U_s^A(\vec{x}) + \lambda_m U_s^B(\vec{x'}) + U_e, \tag{3}$$

where $U_s^A(\vec{x})$ and $U_s^B(\vec{x'})$ represent the unique portions of the energy terms for the two end point chemical species A and B. It should be noted that Equation 3 can also be expressed in a nonlinear form, such as in the form of the soft-core potentials . Therefore, Equation 3 can be generalized as

$$U = f(\vec{x}, \vec{x'}, \lambda) + U_e, \tag{4}$$

in which we have the constraints of $f(\vec{x}, \vec{x'}, 0) = U_s^A(\vec{x})$ and $f(\vec{x}, \vec{x'}, 1) = U_s^B(\vec{x'})$ to recover the chemical end states; the scaled portions have the independent coordinates $\vec{x}$ and $\vec{x'}$, the corresponding potentials of which are scaled in the opposite directions. Here, for simplicity, the discussions will be based on the linear one, Equation 3. As mentioned above, λ and $(1 - \lambda)$ become the labels of the local effective temperatures concomitant with their roles as the potential scaling parameters in the original alchemical free energy simulation design. In this case, the SS algorithm can still be applied, except that here, the energy derivative $\frac{\partial U}{\partial \lambda}$ is equal to $U_s^B(\vec{x'}) - U_s^A(\vec{x})$, when Equation 2 is applied. Consequently, when the λ_m histogram is flattened, free energy difference between any two λ_m states can be naturally obtained according to the following formula

$$\Delta A(\lambda_0 \rightarrow \lambda_1) = -RT[a(\lambda_1) - a(\lambda_0)] = -RT \ln \left(\frac{f(\lambda_1)}{f(\lambda_0)} \right), \tag{5}$$

where $a(\lambda_m)$ and $f(\lambda_m)$ respectively represents the weight function and biasing probability function values. And the time evolution of this computed free energy is expected to behave like in Figure 2b.

Technically, it is very difficult to reach the absolute flatness for the λ_m histogram in order to apply Equation 5, because with the histogram flattened, the modification factor f becomes smaller and its capability to flatten the λ_m histogram is correspondingly reduced. A revised procedure can be used by turning the modification factor f to 1, after it is smaller

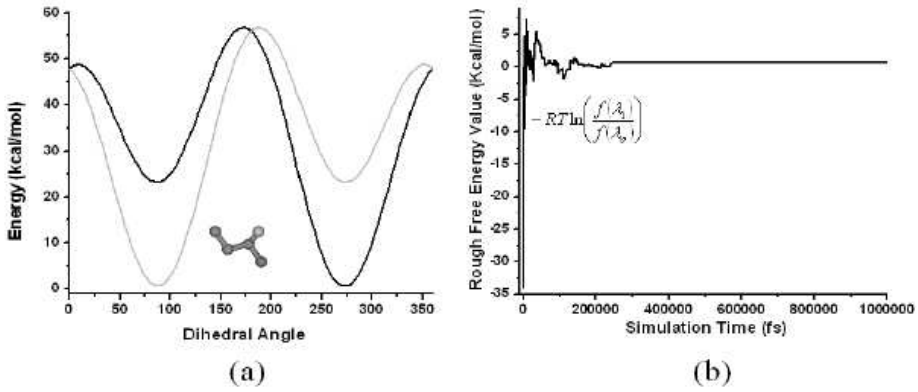


Figure 2. (a) Model potentials set to compute the free energy difference between two "butane-like" molecules. (b) Time evolution of rough free energy, estimated based on Equation 5.

than a pre-set cutoff value. When the modification factor f is 1, the biasing probability function $f(\lambda_m)$ will be constant thereafter and all the ensemble property calculations based on the cumulated histogram $H(\lambda_m)$ are statistically meaningful. Therefore, theoretically exact alchemical free energy value can be estimated using the following equation:

$$\Delta A(\lambda_0 \rightarrow \lambda_1) = -RT \ln \left(\frac{f(\lambda_1)}{f(\lambda_0)} \frac{H(\lambda_1)}{H(\lambda_0)} \right), \tag{6}$$

where $f(\lambda_m)$ is the biasing probability function value for λ_m, when the modification factor f is turned to 1; and $H(\lambda_m)$ is the corresponding accumulated histogram value, counted after the modification factor f is turned to 1.

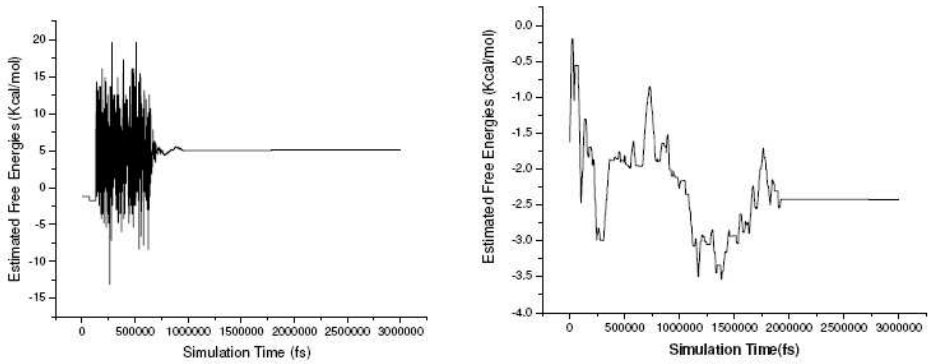
Illustrative Example. For the purpose of demonstrating a simultaneous sampling enhancement accompanying free energy simulation in this method, a model system is set to compute the free energy difference between two end point chemicals with the dihedral potentials of $U = 12\{1 + \cos[\phi \pm 110^0]\} + 20\{1 + \cos(2\phi)\}$. As shown in Figure 2a, these two potentials are symmetric with two asymmetric energy wells each. Correctly obtaining free energy difference between these two butane molecules, theoretical value of which is zero, is very challenging, because existing energy barriers are not trivial to be crossed by thermal activations. By regular canonical ensemble treatments, computed free energy difference was yielded to be 22.47 kcal/mol, which is equal to the difference between global minimum of one molecule and local minimum of the other. As shown in Figure 2, because it can simultaneously enhance sampling, DTA-SS simulation allows rough free energy value, estimated based on Equation 5, to reach the region of zero kcal/mol in 2.5 ps and evolve to be 0.2 kcal/mol with small fluctuation in about 16 ps. Finally, after totally 1 ns simulation, based on Equation 6, exact free energy is estimated to be 0.09 kcal/mol.

4 Hybrid Potential Space Random Walk to Robustly Realize QM/MM Based Simulated Scaling Simulations

The generalized ensemble algorithms can be robustly applied to the systems treated with classical energy potential functions (or called molecular mechanical (MM) potentials), which are usually described as the sum of a series of geometry-dependent functional energy terms, because in these types of potentials, energies can be robustly evaluated regardless of structural qualities, and chemical space is restrictedly pre-determined by the definition of atom types and connectivities. However, direct application of these generalized ensemble methods to the simulations treated with quantum mechanical (QM) potentials (pure QM potential or its hybrid with molecular mechanical potential (QM/MM)) can be problematic and sometimes almost impossible in commonly applied finite-time-step molecular dynamics settings, for the fact that the convergence of the self-consistent-field (SCF) calculation for QM energy evaluation is very structure-sensitive; it can be more demanding than the requirement for the ordinary differential equation propagation stability in molecular dynamics simulations. If generalized ensemble algorithms are directly applied in the QM-based (QM or QM/MM) simulations, instantaneously twisted molecular structures, inevitably generated due to high temperature (or high effective "temperature" corresponding to a low scaling parameter λ value) activations, may make electronic structural SCF calculations difficult to converge or artificially converge to other electronic structural species (effectively like the occurrence of chemical reactions). Although facing such challenge, the increasing demands of accurate calculation of free energy values urgently require robust and efficient QM-based free energy simulation methods. In order to reconcile such confliction between a necessary activation (either by increasing temperature or lowering scaling parameter λ) and the structure-sensitivity nature of QM calculations, one of possible solutions is to avoid direct walking between the activated MM states (with low λ values or high temperatures) and the state requiring QM energy and force calculations in the simulated scaling method design.

Theoretical Design of the Method. Following the same thought in one of our recent works [12], we can design the following hybrid traveling path from QM0 to MM0, then from MMo to MM1, and the from MM1 to QM1, instead of a simple path scaled by one scaling parameter as introduced in one of PI's previous developments. In this hybrid potential space, two end points are our target QM/MM states and the center path from MM0 to MM1 is the same as our classical potential based simulated scaling method.

In this scheme, we need to realize a random walk in a hybrid path rather than a single street. To do so, all the equations in the simulated scaling method can still apply, except for the expression of $\frac{\partial U}{\partial \lambda}$ in Equations 1 & 2. The values of $\frac{\partial U}{\partial \lambda}$ depend on which portion of the path the simulation is currently located in. If the simulation is in the path starting at QM0 and ending at MM0, this value should be equal to $U_{MM0} - U_{QM0}$; if the simulation is in the path starting at MM0 and ending at MM1, this value should be equal to $U_{MM1} - U_{MM0}$; if the simulation is in the path starting at MM0 and ending at MM1, this value should be equal to $U_{QM1} - U_{MM1}$. As noted earlier, Equations 1 & 2 are based on linear scaling equation. As the matter of fact, any nonlinear scaling potentials can be applied to the simulated scaling simulations. Then, these equations can be easily modified. In the original simulated scaling method implementation, soft-core potentials have been successful included, tested, and even employed for practical biomolecular studies.



(a) (b)

Figure 3. (a) Time dependent free energy difference between methanol and methane in gas phase; (b) Time dependent free energy difference between methanol and methane in the solution.

Illustrative Example. A model system is set to compute the solvation free energy difference between methoal and ethane. Here, QM/MM potential was employed; the solutes are treated with the SCCDFTB method and the solvent molecules are treated with the TIP3P model.

As shown in Figure 3, QM/MM based solvation free energy difference value can be efficiently predicted for methanol and ethane. The predicted solvation free energy difference, -7.2 kcal/mol, reproduces experimental values nicely.

References

1. D. L. Beveridge and F. M. Dicapua, Ann. Rev. Biophys. Chem. **18**, 431, 1989.
2. P. Kollman, Chem. Rev. **93**, 2395, 1993.
3. J. M. Rickman and R. LeSar, Annu. Rev. Mat. Res. **32**, 195, 2002.
4. T. Simonson, G. Archontis, and M. Karplus, Acc. Chem. Res. **35**, 430, 2002.
5. Free Energy Calculations: Theory and Applications in Chemistry and Biology, Springer Series in Chemical Physics (Eds. A. Pohorille and C. Chipot) (2007).
6. S. A. Adcock and J. A. McCammon, Chem. Rev. **106**, 1589, 2006.
7. W. Yang, H. Nymeyer, H.-X. Zhou, B. A. Berg, and R. Brüschweiler, J. Comp. Chem. **29**, 668, 2008.
8. H. Li, M. Fajer, and W. Yang, J. Chem. Phys. **126**, 024106, 2007.
9. S. Duane, A. D. Kennedy, and B. J. Pendleton, and D. Roweth, Phys. Lett. B **195**, 216, 1987.
10. F. Wang and D. P. Landau, Phys. Rev. Lett. **86**, 2050, 2001.
11. W. Kwak and U. H. E. Hansmann, Phys. Rev. Lett. **95**, 138102, 2005.
12. H. Li and W. Yang, J. Chem. Phys. **126**, 11410, 2007.